Nephrogenic syndrome of inappropriate antidiuresis

Elena N. Levtenchenko and Leo A.H. Monnens

1Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium and 2Department of Physiology, Radboud University Nijmegen Medical Centre Nijmegen, The Netherlands

Correspondence and offprint requests to: Elena N. Levtenchenko; E-mail: elena.levtenchenko@uzleuven.be, e.levtchenko@kunc.umcn.nl

Abstract

The nephrogenic syndrome of inappropriate antidiuresis (NSIAD) is a rare, recently recognized disorder in water balance affecting not only infants but also adults. A new molecular mechanism responsible for NSIAD has recently been identified: a gain of function of the arginine vasopressin (AVP) receptor type 2 (V2R), causing the constitutive activation of the receptor. Clinical presentation and laboratory findings of NSIAD resemble those of the syndrome of inappropriate secretion of antidiuretic hormone and consist of hyponatraemia, seizures and the lack of urinary dilution; however, the AVP levels in plasma are undetectable or very low. An elucidation of the pathophysiology of this syndrome will provide more insight into the action of AVP. An effective treatment of NSIAD is available. It consists of fluid restriction and administration of oral urea. Reported experience with furosemide treatment in NSIAD is still lacking.

Keywords: antidiuresis; hyponatraemia; NSIAD; SIADH; V2R

Introduction

The first cases of inappropriate antidiuresis can be ascribed to Schwartz et al. [1], who reported two patients with bronchogenic carcinoma having marked hyponatraemia but still slightly hypertonic urine, indicating inappropriate urinary concentration. The different causes and criteria for the diagnosis of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) were further adequately presented by Ellison and Berl [2] and by Decaux [3]. In 25 patients considered as having SIADH, measurements of plasma arginine vasopressin (AVP) were performed during the infusion of hypertonic saline [4]. Four different patterns of osmoregulatory defects were obtained. At plasma sodium concentration of 135 mEq/L in three of the four patterns, AVP was increased. In two patients, AVP was undetectable at plasma sodium concentration between 120 and 140 mEq/L. Ellison and Berl coined the syndrome of inappropriate antidiuresis for these two patients. A prolonged exposure to AVP results in the loss of hydro-osmotic effect of AVP (or so-called AVP escape).
This phenomenon has been studied in rat models, showing a downregulation of AVP receptor binding, associated with decreased expression of aquaporin 2 in the collecting duct [5]. Hoorn et al. [6] used combined proteomics and bioinformatic pathways analysis of the collecting duct during the escape from AVP. Immunoblotting showed the known decrease in aquaporin 2 expression, but also a decrease in the abundance of the urea transporter UT-A3. Under normal circumstances, UT-A1 (localized to the apical membrane) and UT-A3 (localized to the basolateral membrane) are involved in urea reabsorption from the inner medullary collecting duct to the inner medullary interstitium. AVP increases the UT-A3 expression at the basolateral membrane, thus increasing medullary osmolarity [7]. The mechanisms identified in animal models are probably responsible for AVP escape in humans with SIADH.

Nephrogenic syndrome of inappropriate antidiuresis (NSIAD)

Feldman et al. [8] described in 2005 two unrelated male infants with a clinical presentation and laboratory findings of SIADH, but with undetectable AVP levels in plasma, resembling type 4 pattern of osmoregulatory defects defined by Robertson [4]. In these patients, they could demonstrate a constitutive activation of the X-linked V2 vasopressin receptor (V2R). DNA sequencing of the V2R gene identified in both infants missense mutations resulting in the substitution of arginine to cysteine or leucine in codon 137 (Figure 1).

More data on currently well-documented reports of infants with NSIAD are presented in Table 1 [8–11]. Some

### Table 1. Summary of reported NSIAD patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Mutation</th>
<th>Age at presentation</th>
<th>Clinical symptoms</th>
<th>Serum sodium mmol/L</th>
<th>Serum osmolality mOsm/kg</th>
<th>Plasma AVP pg/mL</th>
<th>Urine sodium mmol/L</th>
<th>Urine osmolality mOsm/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feldman et al. [8]</td>
<td>Codon 137 arginine to cysteine</td>
<td>3 months</td>
<td>Irritability</td>
<td>123</td>
<td>252</td>
<td>&lt;1</td>
<td>35</td>
<td>284</td>
</tr>
<tr>
<td>Feldman et al. [8]</td>
<td>Codon 137 arginine to leucine</td>
<td>2.5 months</td>
<td>Generalized seizures</td>
<td>118</td>
<td>247</td>
<td>&lt;1</td>
<td>75</td>
<td>390</td>
</tr>
<tr>
<td>Bes et al. [9]</td>
<td>Codon 137 arginine to cysteine</td>
<td>5 months</td>
<td>Generalized seizures</td>
<td>124</td>
<td>261</td>
<td>&lt;1</td>
<td>25</td>
<td>468</td>
</tr>
<tr>
<td>Marcialis et al. [10]</td>
<td>Codon 137 arginine to cysteine</td>
<td>Neonatal period?</td>
<td>Seizures</td>
<td>NA</td>
<td>NA*</td>
<td>Normal range</td>
<td>NA*</td>
<td>NA*</td>
</tr>
<tr>
<td>Gupta et al. [11]</td>
<td>Codon 137 arginine to cysteine</td>
<td>7 months</td>
<td>Generalized seizures</td>
<td>120</td>
<td>247</td>
<td>0.7</td>
<td>130</td>
<td>309</td>
</tr>
<tr>
<td>Cho et al. [29]</td>
<td>Codon 137 arginine to cysteine</td>
<td>2 months</td>
<td>Vomiting</td>
<td>129</td>
<td>260</td>
<td>&lt;0.6</td>
<td>NA*</td>
<td>506</td>
</tr>
<tr>
<td>Cho et al. [29]</td>
<td>Codon 137 arginine to cysteine</td>
<td>22 months</td>
<td>Seizures</td>
<td>124</td>
<td>265</td>
<td>1.43</td>
<td>NA*</td>
<td>950</td>
</tr>
</tbody>
</table>

*NA: not applicable.*
conclusions can be gleaned from these data. Most of the infants present with seizures and have clearly low serum sodium levels with lack of the expected dilution of the urine. Not all infants with the activating mutations have undetectable AVP levels in plasma. This information implies that the indications for screening of infants for the activating V2R mutations should be extended. Clinical symptoms mostly become apparent after the age of a few months. In our opinion, the neonatal symptoms of the patient described by Marcialis et al. [10] might be related to neonatal asphyxia. The limitation of the concentrating capacity at a very young age together with their high insensible water loss may have a protective role in the early postnatal period and postpone the appearance of the NSIAD symptoms [12].

A large five-generation family with NSIAD was reported by Decaux et al. [13]. The activating mutation was detected in three hemizygous males and four heterozygous females. All of them were diagnosed as adults (see also Soule et al. [14]). X-inactivation in the female heterozygous patients will result in a constitutive active V2R in one-half of the collecting duct cells, causing symptoms of NSIAD. The same mechanism is responsible for the clinical phenotype of nephrogenic diabetes insipidus in females heterozygous for V2R receptor mutation [15]. In an asymptomatic heterozygous female patient carrying activating V2R mutation, a skewed inactivation preferentially of the mutant gene is a plausible explanation of the absence of the symptoms. As Decaux et al. [13] already stated, the condition of NSIAD might remain unrecognized until advanced age. Clark et al. demonstrated impaired free water excretion after water loading at an older age [16]. Thus, an increase in the degree of inappropriate antidiuresis, when challenged with water, can be expected in elderly people with NSIAD.

Pathophysiology of NSIAD

In healthy subjects, arginine vasopressin (AVP) binding to the V2R stimulates cAMP production through the Gαs and adenyl cyclase. Subsequent phosphorylation of AQP2 by the cAMP-dependent protein kinase (PKA) is suggested to promote the insertion of AQP2 into the apical membrane of the principal cells of renal collecting duct, resulting in enhanced reabsorption of free water [17]. The ability of the mutant V2R to induce cAMP, as measured by cAMP-inducible luciferase reporter in COS-7 cells, was 4–7.5-fold increased compared with the wild-type V2R [8]. This gain of function due to constitutive activation of V2R in NSIAD patients explains inappropriate antidiuresis.

All mutations described in NSIAD so far involve the arginine residue at the position 137 [8–11]. This residue is highly conserved and is a part of the DRY/H motif, located at the junction of the third transmembrane domain and the second intracellular loop (Figure 1). The V2R-R137C and V2R-R137L mutants traffic more efficiently to the plasma membrane compared with the V2R-R137H mutant. The latter mutation is a cause of nephrogenic diabetes insipidus (NDI) due to impaired trafficking [17].

Normally, G-protein-mediated signalling is a subject of extensive negative regulation. A decrease in the negative regulation would prolong the cellular response to an activated receptor. Upon binding of AVP, multiple serine residues in the V2R terminus are phosphorylated by G-protein-coupled receptor kinases [18]. The phosphorylated receptors recruit arrestins. Arrestin binding to activated receptors promotes desensitization by interrupting receptor–G-protein coupling, with simultaneously recruiting of the clathrin-dependent endocytotic machinery and lysosomal degradation [19]. It was hypothesized that activating V2R mutants might have impaired β arrestin binding. However, using bioluminescence resonance energy transfer and confocal microscopy, Kocan et al. [18,19] demonstrated that the activated mutants interacted with β arrestin2 in an agonist-independent manner. It is likely that these mutant receptors are subsequently transported to late endosome/lysosomes analogous to the activated wild-type receptor [19]. Thus, impaired arrestin binding cannot explain the constitutive activation of the V2R.

Recent study has further characterized V2R-R137H (causing NDI) compared with V2R-R137C and V2R-R137L (causing NSIAD) [20]. All three mutants showed both impaired maturation (reduced Golgi processing) and elevated constitutional endocytosis resulting in a reduced steady-state surface expression. The elevated endocytosis may reduce the severity of NSIAD. The constitutional activation of V2R-R137C and V2R-R137L remains unexplained. Rochdi et al. [20] propose that the balance between the engagement of Gαs and β arrestin may determine the extent of basal cAMP production causing the difference between NSIAD and NDI mutations.

As the constitutive activation of V2R may also be present in endothelial cells, Feldman et al. [8] measured the concentration of von Willebrand factor (vWF) antigen in plasma of the patients and found a normal concentration with a normal ability of vWF to agglutinate platelets. In our opinion, this interesting observation might be explained by the fact that the majority of circulating vWF is produced by a constitutive uncontrolled pathway [21,22]; therefore, an upregulation of cAMP-induced vWF exocytosis cannot be ruled out by measuring normal circulating vWF levels. In the future, the effect of the administration of epinephrine and histamine should be evaluated in patients with NSIAD by measuring the release of several constituents of Weibel–Palade bodies (WPbs) content such as vWF, interleukin 8, angiopoietin 2 and plasminogen activator. In case of the constitutive activation of V2R on the endothelial cells, a decreased content of WPbs can be expected.

It is, however, not excluded that the constitutive activation of V2R may have a limited effect on the endothelial cells due to the mechanism called tachyphylaxis, which is characterized by a reduced exocytosis after repeated stimulation: after a second dose of DDAVP (6 h later), a rise in vWF is ~30% lower than those obtained after the first dose of DDAVP [23].

Treatment

The different possibilities of treatment of NSIAD are clearly discussed by Gitelman et al. [24]. Fluid restriction
alone, the simplest treatment, is not feasible during infancy as caloric deficiency would be the consequence. AVPR2 inverse agonist SR121463 have been recently tested and failed to decrease the constitutive activity of V2R-c-R137L mutants and increased R137C-V2R cell-surface targeting, consistent with its inactivity in NSIAD patients carrying the R137C-V2R mutation [13,20]. The recent study by Rochdi et al. [20] provided a rational background for the use of AVP in NSIAD patients; they showed that AVP stimulated V2R internalization, beyond already elevated R137C and V2R-R137L endocytosis and did not stimulate cAMP production in cells expressing these mutants [20]. The observed in vitro effect of ADH, however, is rather small, and when high doses are needed, the extra-renal actions on V1a and V1b receptors should be considered. In contrast to the finding by Rochdi et al., Tenenbaum et al. [25] showed a small stimulation of cyclic AMP in COS cells expressing the mutant receptor after application of AVP. Thus, a deleterious effect of AVP in patients with NSIAD cannot be excluded and warrants additional studies, before it can be tested in therapeutic settings.

Also, testing of the effect of non-competitive V2 antagonists still has to be performed [26].

Extensive experience with the use of oral urea [27] or a single oral dose of furosemide with salt supplementation [26] has been reported in patients with SIADH and can be applied in NSIAD patients. Successful use of oral urea has been reported in patients with NSIAD [8,10,13,28]. However, it was surprising that the young children took the oral urea without protesting. After early childhood, the symptoms of NSIAD usually decrease, as children can often self-regulate fluid intake, and all other treatments might be discontinued [29].

Furosemide has not yet been tested in patients with NSIAD, but is of potential benefit, because it decreases the medullar hypertonicity, mitigating the stimulus of the hypertonic environment on the aquaporin 2 expressions in the medullar hypertonicity, mitigating the stimulus of the NSIAD, but is of potential benefit, because it decreases the symptoms of NSIAD usually decrease, as children can often self-regulate fluid intake, and all other treatments might be discontinued [29].

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Conclusion

In a congenital renal tubular disorder, the symptoms are generally expected to be present shortly after birth. This is not the case in NSIAD. Partially protected by the limitation of renal concentrating capacity and high insensible water loss at an early age, patients manifest with clinical symptoms of NSIAD during late infancy or even in adulthood. NSIAD should be suspected in infants with seizures and low plasma sodium and in older patients with inexplicable hyponatraemia, low renin, and aldosterone as well as low AVP levels, accompanied by concentrated urine. Therapy should consist of fluid restriction and eventual administration of the oral urea. Other therapeutic options such as the use of furosemide still have to prove their therapeutic utility. Symptoms of NSIAD may become more prominent at advanced age due to the additional limitation in free water excretion, normally occurring in elderly people.

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References

Proteomic biomarkers in diabetic nephropathy—reality or future promise?

Harald Mischak1,2,* and Peter Rossing3,*

1BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK, 2Mosaicques Diagnostics, Hannover, Germany and 3Steno Diabetes Center, Gentofte, Denmark

Correspondence and offprint requests to: Harald Mischak; E-mail: h.mischak@clinmed.gla.ac.uk

*Member of the European Kidney and Urine Proteomics COST Action (EuroKUP) and of the SysKID consortium.

Keywords: diabetic nephropathy; prognosis; proteomics; urine

In this issue, Ameur et al. [1] present a review on ‘proteomics in diabetic nephropathy’, a very timely subject, given the substantial burden of diabetic nephropathy (DN) and the expected increase in healthcare demand if the current situation does not undergo radical change. The article lists the recent work published in this area and gives a good overview of the field. The main question that is being extensively addressed is: what can proteomics deliver today that may help improving the situation with DN being a global challenge and the leading cause of end-stage renal disease in the Western world, and make a true change in the management of patients? Detection of DN using urinary proteomics is a sensible first goal as a proof-of-principle. Urine proteomics has delivered biomarkers for DN, but the moderate consistency observed between biomarkers reported in different studies is puzzling. This inconsistency is in part attributed to different technologies used that resolve different parts of the proteome: 2D electrophoresis enables assessing the higher molecular weight proteome (>10 kDa), while capillary electrophoresis-coupled mass spectrometry (CE-MS) allows assessing the low-molecular-weight proteome/peptidome [2]. Furthermore, the lack of statistical power resulting in the reporting of artefacts may be another major contributing factor.

When combining the current knowledge on urinary proteomic biomarkers for DN, a significant increase in plasma proteins, including their degradation products, is observed in urine. This likely reflects significant alterations in the filtration barrier, at least in part owed to structural damages of glomeruli and tubuli, and to altered protease activity in DN. A further hallmark is the substantial decrease of extracellular matrix degradation products in urine. While the increase in urinary plasma proteins (or degradation products) may reflect later stages of DN, the changes in extracellular matrix components may indicate early stages and onset of fibrosis [3].

The identification of consistent proteomic changes clearly demonstrates that urine proteomics can deliver ‘biologically significant’ information. From the clinical perspective though, the question remains: can urine proteomics deliver ‘clinically useful’ information that will have a positive (and tangible) impact on patient management? The current clinical challenges in DN that may be approached employing urinary proteomics are: (i) detection of high-risk patients,